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PREPARATION AND CYCLOADDITIONS OF A 4-METHOXY-3-OXIDOPYRYLIUM YLID: A REAGENT FOR THE SYNTHESIS OF HIGHLY SUBSTITUTED SEVEN-MEMBERED RINGS AND TETRAHYDROFURANS

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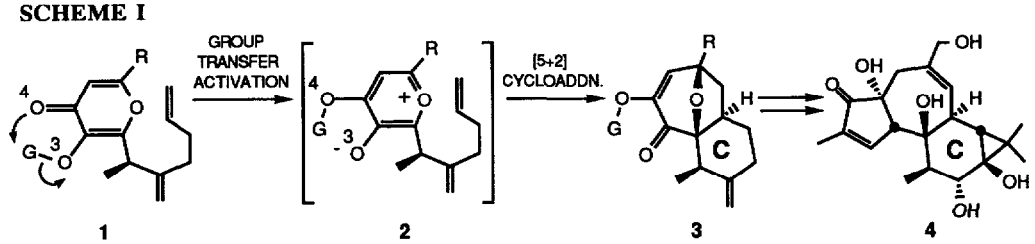
Abstract: The preparation of 4-methoxy-6-methyl-3-oxidopyrylium ylid from α-deoxykojic acid and its cycloaddition behavior as a 5 carbon dipole or carbonyl ylid with various dipolarophiles is described.

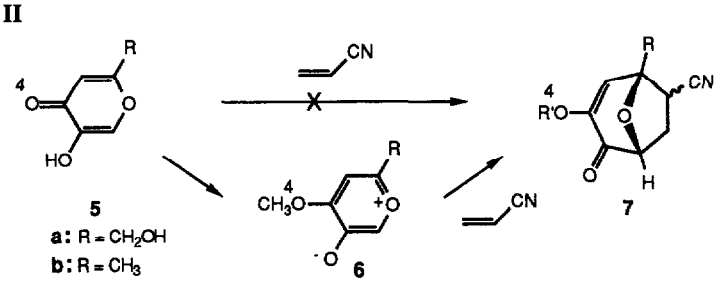
Recently, we reported a synthesis of phorbol (**4**, Scheme I) involving a general route to medicinally important members of the tigliane (phorbol) as well as ingenane and daphnane families.[1] Central to the success of this effort was a [5C+2C] cycloaddition between a 3-silyloxy-4-pyrone and a tethered alkene (**1** to **3**). The key 5C component in this cycloaddition, an oxidopyrylium ylid (**2**), was generated *in situ* through a group transfer activation process, involving migration of the pyrone O-3 group to O-4. Since this *synchronous* group

SCHEME I



transfer activation step is apparently rate limiting and frequently requires high temperatures, it was proposed and found that an alternative but milder activation process can be performed in one operation through a stepwise process in which O-4 is first alkylated and followed by removal of the group at O-3.[2] The success of this process suggests a general solution to a longstanding problem in synthesis exemplified by the finding that commercially available kojic acid (**5a**, Scheme II) and its derivatives (e.g., **5b**) react with alkenes such as acrylonitrile only at elevated temperatures and under these conditions provide only products arising from

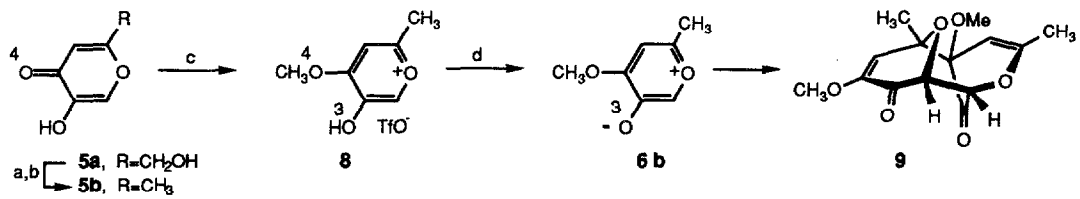
SCHEME II



secondary reactions.[3] We now describe how oxidopyrylium ylid **6b** (and presumably related ylides) can be prepared under mild conditions from readily available **5b** and the performance of this reagent as a 5 carbon dipole (oxypentadienyl cation) or a 3 atom heterodipole (carbonyl ylid) in room temperature intermolecular cycloadditions involving activated π-systems, providing overall a new route to highly oxygenated seven-membered rings as well as tetrahydrofurans.[4,5]

α-Deoxykojic acid (**5b**), used in this study as a representative substrate, was prepared from commercially-available kojic acid (**5a**, Scheme III) in two steps.[6] Reaction of **5b** with MeOTf (O-4 alkylation) provided the pyrylium salt **8**,[7] which upon treatment with a hindered base (O-3 group removal) afforded the desired 3-oxidopyrylium zwitterion **6b**, as evidenced by its efficient dimerization to **9** (80% yield).

SCHEME.III



(a) $SOCl_2$, $CHCl_3$, reflux; (b) H_2, Pd/C, NaOAc, MeOH; (c) MeOTf (1.5 equiv), CH_2Cl_2, reflux, 4h; (d) 2,2,6,6-tetramethylpiperidine.

Attempts to intercept **6b** before it dimerized were initially conducted with strongly activated olefins. As a first procedure (**Method A**), base was added to a solution of reagent **8** and dipolarophile. Thus, when 2,2,6,6-tetramethylpiperidine (TMP) was added to a dichloromethane solution of the pyrylium salt **8** and N-phenylmaleimide (3 equiv) and the reaction stirred for 4 hours at room temperature, cycloadducts **10** and **11** (Scheme IV) were obtained as a 1.8:1 mixture of the *exo:endo* isomers in 65 % overall yield.[8] Analogously, the cycloadduct **12** was prepared in 60 % yield from dimethyl acetylenedicarboxylate (DMAD).[9] While these experiments clearly demonstrate that kojic acid derivatives can be used to generate oxidopyrylium ylides and that the latter can be trapped intermolecularly, reactions of the ylid with less reactive dipolarophiles were still complicated by competitive formation of the ylid dimer. For example, when acrylonitrile was used as the trapping agent, only a trace amount of the cycloadduct was detected, the major product being the dimer **9**.[10]

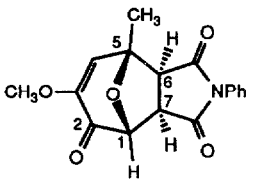
Since the formation of dimer is obviously favored by a high ylid concentration, it was reasoned that the slow addition of **8** to a solution of dipolarophile and a compatible base would serve to keep the ylid concentration low, thereby allowing for its competitive cross reaction with the dipolarophile. This strategy (**Method B**) proved indeed to be effective. When a solution of the pyrylium salt **8** was slowly added (over approx. 4 h) to a mixture of the N-phenylmaleimide and TMP, cycloadducts **10** and **11** were again produced but in an improved yield of 73%. More significantly, when acrylonitrile was used as dipolarophile, a 2.3:1 mixture of the 6-*exo* (**13**) and 6-*endo* (**14**) cycloadducts was produced in 45 % yield (Scheme IV).[11]

The results of the above experiments suggested a third method to control the concentration of the reactive ylid (**Method C**). Specifically, it was proposed that if a base weaker than TMP were used, the concentration of the reactive ylid would be decreased and its dimerization reaction would therefore be retarded. Pyridine bases (2,6-di-*t*-butyl-4-methylpyridine and 2,4,6-trimethylpyridine) were found to slow the dimerization process, but the cycloadducts from N-phenylmaleimide and acrylonitrile were obtained in low yield. However, when dimethylaniline was used, excellent yields of the cycloadducts were obtained from N-phenylmaleimide, DMAD,

and even the less reactive dipolarophile acrylonitrile (Table I).

Several other types of dipolarophiles were also tried. The less reactive styrene provided a 1:2.2 mixture of the 6-*exo:endo* stereoisomers **15** and **16**.[12] Norbornene, a strained olefin, also reacted efficiently as a dipolarophile, affording a single adduct (**17**) in 73% yield.[13] Ethyl vinyl ether reacted rapidly in the presence of the pyrylium salt but only polymeric materials were observed in this case. Non-activated alkenes such as cyclohexene, cyclohexenone and isoprene failed to react, as did vinyl acetate. The heterodipolarophile benzaldehyde was also unreactive.

SCHEME IV



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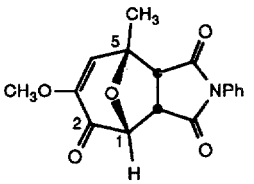

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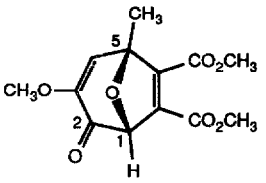

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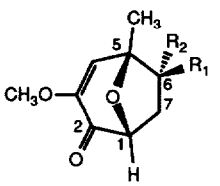

13, R_1 = CN, R_2 = H
14, R_1 = H, R_2 = CN
15, R_1 = Ph, R_2 = H
16, R_1 = H, R_2 = Ph

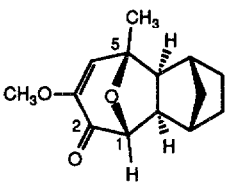

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TABLE I

Dipolarophiles[a]	Isolated yield	Products	(exo:endo)
DMAD	73 %	**12**	
N-phenylmaleimide	98 %	**10/11**	(1.8 : 1)
acrylonitrile	78 %	**13/14**	(2.3 : 1)
styrene	58 %	**15/16**	(1 : 2.2)
norbornene	73 %	**17**	(1 : 0)

a) 5-20 equiv of dipolarophile used. Reaction time: 10 - 30 h.

In conclusion, we have shown that the parent 4-methoxy-6-methyl-3-oxidopyrylium ylid (**6b**) can be easily prepared under mild conditions from the corresponding kojic acid derivative **5b** using three different methods (**A**-**C**) and that this ylid undergoes efficient cycloaddition reactions with activated dipolarophiles at room temperature, providing adducts which in some cases have been previously inaccessible. In the laboratory, this methodology offers an off-the-shelf reagent (**8**) which is trivially converted into an intermediate (**6b**) that serves as a 5-carbon dipole or a heterodipole for [5+2] or [3+2] additions across activated π-systems. PMO theory, which has previously been used to explain the site, regio- and stereoselectivity of related cycloadditions,[4,5] accommodates the results of the reactions presented in this communication, providing overall a predictive and

practical route to new cycloadducts. The adducts produced in these reactions are rigid bicyclic systems whose rich, but differentiated functionalization and facial biases offer the potential of servicing numerous problems in the synthesis of complex seven-membered rings as well as tetrahydrofurans.

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6. Hurd, C. *J. Org. Chem.* **1958**, 1276, and Brown, M. C. *J. Chem. Soc.* **1958**, 2558.
7. This salt crystallized from EtOAc as a white solid (m.p. 52°C).
8 The *endo* isomer is defined as that in which the olefinic substituent(s) is *anti* to the oxido-bridge. The stereochemistry of adducts **10** and **11** was deduced from the coupling constant across the positions 1,7.
9. All new compounds gave satisfactory NMR and high resolution mass spectra.
10. The regio- and stereochemistry of the dimer follow from the ^{1}H NMR spectrum, which shows a coupling constant of 2.5 Hz between the protons α to the ketones.
11. ^{1}H NMR ($CDCl_3$, 300 MHz) **13** (6-*exo*): 5.83 (s, 1H), 4.75 (br d, J=8.6 Hz, 1H, H-1), 3.62 (s, 3H), 3.15 (dd, J=3.4 and 9.2 Hz, 1H, H-6), 2.75 (ddd, J=3.4, 8.7 and 14 Hz, 1H, H-7$_{exo}$), 2.31 (dd, J=9.3 and 14 Hz, 1H, H-7$_{endo}$), 1.82 (s, 3H). **14** (6-*endo*): 5.94 (s, 1H), 4.68 (br d, J=7.7 Hz, 1H, H-1), 3.69 (s, 3H), 2.81-3.0 (m, 2H, H-6 and H-7$_{exo}$), 2.12 (br dd, J~4.0 and 14 Hz, 1H, H-7$_{endo}$), 1.74 (s, 3H).
12. ^{1}H-NMR ($CDCl_3$, 300 MHz) **15** (6-*exo*): 7.18-7.38 (m, 5H), 5.95 (s, 1H), 4.79 (br d, J~7.3 Hz, 1H, H-1), 3.64 (s, 3H), 3.30 (dd, J=3.3 and 8.8 Hz, 1H, H-6), 2.55 (ddd, J~3.3, 7,9 and 14 Hz, 1H, H-7$_{exo}$), 2.45 (ddd, J=1.7, 8.8 and 14 Hz, 1H, H-7$_{endo}$), 1.10 (s, 3H). **16** (6-*endo*): 7.29 (m, 3H), 7.17 (m, 2H), 5.34 (s, 1H), 4.70 (dd, J=1.8 and 8.8 Hz, 1H, H-1), 3.55 (s, 3H), 3.31 (dd, J=7.1 and 10.1 Hz, 1H, H-6), 2.93 (m, 1H, H-7$_{exo}$), 2.01 (ddd, J=1.8, 7.1 and 13 Hz, 1H, H-7$_{endo}$), 1.54 (s, 3H).
13. The *syn* configuration (with the generated bonds syn to the methylene bridge) was deduced from the shielding of one of the C-13 protons by the oxygen bridge (doublets at δ 1.8 and δ 0.99). Concerning the stereochemistry of a related cycloadduct see ref. 4b. ^{1}H-NMR ($CDCl_3$, 300 MHz) of **17**: 5.90 (s, 1H), 4.29 (s, 1H), 3.58 (s, 3H), 2.35 (br d, J~12 Hz, 2H), 1.98 (br s, 2H), 1.84 (br d, J~9.8 Hz, 1H), 1.5 (m, 5H), 1.12 (m, 2H), 0.99 (br d, J~9.6 Hz, 1H).

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